REMARKS

Introduction

Receipt is acknowledged of an office action dated July 2, 2003. In the action, the examiner rejected claim 1 allegedly for indefiniteness, claims 1-16, 18, 20-38, 40-42, 46 and 50-54 as allegedly obvious over Gustavson *et al.* (U.S. Patent No. 5, 420,105) ("Gustavson '105") in view of Gustavson *et al.* (U.S. Patent 5,283,342) ("Gustavson '342") and Maddock (U.S. Patent No. 5,474,772), and claims 37-39 and 44 as allegedly obvious over Gustavson '105. Furthermore, the examiner objected to claims 17, 19 and 47-49 for being dependent on a rejected base claim.

Claims 1-42, 44 and 46-54 are pending in the present application.

35 U.S.C. § 112, second paragraph

With regard to claim 1, section A, the examiner's understanding of the section is correct. Concerning claim 1, section C, the composition comprises one of the following: (1) a second therapeutic agent or (2) a second conjugate that comprises a low molecular weight hapten and a second therapeutic agent. Applicants believe that the claimed invention is unambiguous. Indeed, the examiner appears to understand the presently claimed invention. However, if the examiner still feels that the claims are indefinite, applicants respectfully request that the examiner suggest appropriate claim language.

35 U.S.C. § 103

The examiner rejected claims 1-16, 18, 20-38, 40-42, 46 and 50-54 as allegedly obvious over Gustavson '105, in view of Gustavson '342 and Maddock. In particular, the examiner asserted that "[i]t would have been obvious...to modify the invention of Gustavson et al (US Patent No. 5,420,105) using the teachings of Gustavson et al (US Patent No. 5,283,342) and Maddock and generate compositions set forth in independent claims 1, 37, and 38..." (office action at 6).

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references (or references when combined) must teach or suggest all the claim limitations. See MPEP 2142. Applicants respectfully assert that the examiner has not met her burden.

The polymer-drug conjugates recited in the present invention are attached to recognition haptens and recognized by a second arm of a multispecific antibody. In other words, the polymer-drug conjugates are not attached to the antibodies themselves. In addition, the therapeutic agent of the instant invention claims is covalently bound to a polymeric carrier.

This is in contrast to Gustavson '105, which describes a covalently associated therapeutic agent. Indeed, the Gustavson '105 invention is directed to the use of drug-polymer conjugates wherein the drug is not covalently bound to the polymer, but is instead associated with the polymer by an inserted protein sequence. This is shown in example 5, by use of a riboflavin-binding protein fragment to bind an anthracycline such as doxorubicin. *See*, for example, col. 23, example 5 of the '105 patent. In addition, Gustavson '105 teaches that a therapeutic agent can be delivered, site-specifically, by attaching the drug-polymer conjugate covalently to an antibody via a linkage between the polymer and the antibody. See, col. 2, lines 55-65 of the '105 patent. The present invention does not claim attaching a polymer to an antibody.

Gustavson '342 is primarily directed to pretargeting methods, wherein a therapeutic agent is delivered to a target site in the second or third step of a two or three step method. Column 5 of Gustavson '342 teach an alternative two-step method, wherein the first step comprises the administration of a targeting moiety conjugated to a therapeutic agent and a ligand (biotin), and the second step comprises the administration of an anti-ligand (avidin). The anti-ligand binds to the ligand, cross-linking the targeting moiety-ligand-therapeutic agent conjugate, and inducing internalization of the conjugate. This embodiment is exemplified as the "second alternative protocol" in Example X at col. 23, lines 11-15.

Although this embodiment of Gustavson '342 uses a conjugate comprising a targeting moiety, a first member of a binding pair, and a first therapeutic agent, as recited in independent claims 37 and 38, no second therapeutic agent is administered. In fact, both Gustavson patents do not teach administration of two distinct therapeutic agents.

In addition, Gustavson '105 and '342 do not teach the use of a naked antibody as a therapy agent. However, some of the instantly rejected claims are drawn to a composition that comprises a naked antibody, and the naked antibody is one of two therapy agents. This feature is not taught in the Gustavson patents.

Regarding Maddock '772, this reference relates to the removal of therapeutic agents from the circulating blood of patients by use of extracorporeal methods such as immunoabsorption. This is unrelated to the instant invention. Accordingly, the combination of Maddock with Gustavson '105 and Gustavson '342 does not teach or suggest all the claim limitations of the present invention.

Continuing, the examiner rejected claims 37-39 and 44 as allegedly obvious over Gustavson '105. In particular, the examiner asserted that Gustavson "fails to specifically state that a radionuclide may be present" and that "it would be obvious to one of ordinary skill in the art...to incorporate a radionuclide" (office action at 8). For the reasons discussed above, Gustavson does not render the present invention obvious, regardless of whether or not Gustavson teaches a radionuclide.

The claims of the present invention are directed to two separate therapy steps comprising the use of a multispecific antibody. Gustavson '105 does not teach compositions comprising two therapeutic agents administered in two distinct steps as described in the instant invention. In fact, only a single therapy step is disclosed in Gustavson '105, where a composition that contains a therapeutic agent is delivered directly by an antibody conjugate, or separately, after antibody-avidin pretargeting (and then followed by delivering a therapy-agent-polymer-biotin).

In addition, Gustavson '105 describes "polymeric carriers comprising at least one drug-binding domain derived from a protein, wherein each drug-binding domain can non-

covalently bind a drug" ('105 patent, col. 2, lines 47-50). Indeed, this reference addresses the "need in the field of drug conjugation to be able to attach multiple drug molecules to the targeting antibody, ligand or anti-ligand without covalent modification of the drug and loss of drug activity" (id. at col. 2, lines 40-44).

As such, the therapeutic agent of Gustavson '105 is not covalently bound to the carrier polymer. The Gustavson invention is directed to the use of drug-polymer conjugates wherein the drug is not covalently bound to the polymer, but is instead associated with the polymer by an inserted protein sequence. This is exemplified by use of a riboflavin-binding protein fragment to bind an anthracycline such as doxorubicin. *See*, for example, col. 23, example 5 of the '105 patent. In addition, Gustavson '105 teaches that a therapeutic agent can be delivered, site-specifically, by attaching the drug-polymer conjugate covalently to an antibody via a linkage between the polymer and the antibody. See, col. 2, lines 55-65 of the '105 patent.

In addition, claim 44 recites that the targeting moiety comprises a naked antibody, and the therapeutic agent is the same as said naked antibody. However, Gustavson '105 does not teach a naked antibody as a therapeutic agent.

Claim Objections

The examiner objected to claims 17, 19 and 47-49 as being dependent on a rejected base claim but deemed the claims allowable if rewritten in independent form. Applicants believe that the claims from which claims 17, 19, and 47-49 depend are allowable in view of the foregoing and therefore, applicants do not believe that amending claims 17, 19 and 47-49 is necessary.

CONCLUSION

It is respectfully urged that the present application is now in condition for allowance. Early notice to that effect is earnestly solicited.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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